(FILE 'HOME' ENTERED AT 16:27:18 ON 11 DEC 2002)

FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE' ENTERED AT 16:27:24 ON 11 DEC 2002

L1	212	EARLY GROWTH RESPONSE FACTOR
L2	4842	EGR-1
L3	4160	ISCHEMIC TISSUE
L4	112620	REPERFUSION
L5	77394	ANTISENSE
L6	15271	RIBOZYME
L7	0	L1 AND L3 AND L4
L8	4	L2 AND L3 AND L4
L9	1	DUP REM L8 (3 DUPLICATES REMOVED)
L10	20	L1 AND L5
L11	8	DUP REM L10 (12 DUPLICATES REMOVED)
L12	0	L11 AND L3
L13	0	L11 AND L4
L14	2	L1 AND L6
L15	214	L2 AND L5
L16	97	DUP REM L15 (117 DUPLICATES REMOVED)
L17	0	L16 AND L3
L18	0	L16 AND L4
L19	14	L2 AND L6
L20	14	DUP REM L19 (0 DUPLICATES REMOVED)
L21	0	L20 AND L3
L22	0	L20 AND L4
L23	353820	ISCHEMIA
L24	3402544	TISSUE
L25	65269	L23 AND L24
L26	3	L25 AND L1
L27	3	DUP REM L26 (0 DUPLICATES REMOVED)
L28	39	L25 AND L2
L29	19	DUP REM L28 (20 DUPLICATES REMOVED)

L9 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2001:58823 BIOSIS
DOCUMENT NUMBER: PREV200100058823
TITLE: **Egr-1**, a master switch coordinating upregulation of divergent gene families underlying ischemic stress.
AUTHOR(S): Yan, Shi-Fang (1); Fujita, Tomoyuki; Lu, Jiesheng; Okada, Kenji; Zou, Yu Shan; Mackman, Nigel; Pinsky, David J.; Stern, David M.
CORPORATE SOURCE: (1) Department of Surgery, Columbia University, 630 West 168th Street, New York, NY: sy18@columbia.edu USA
SOURCE: Nature Medicine, (December, 2000) Vol. 6, No. 12, pp. 1355-1361. print.
ISSN: 1078-8956.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Activation of the zinc-finger transcription factor early growth response (**Egr**)**-1**, initially linked to developmental processes, is shown here to function as a master switch activated by ischemia to trigger expression of pivotal regulators of inflammation, coagulation and vascular hyperpermeability. Chemokine, adhesion receptor, procoagulant and permeability-related genes are coordinately upregulated by rapid ischemia-mediated activation of **Egr-1**. Deletion of the gene encoding **Egr-1** strikingly diminished expression of these mediators of vascular injury in a murine model of lung ischemia/ **reperfusion**, and enhanced animal survival and organ function. Rapid activation of **Egr-1** in response to oxygen deprivation primes the vasculature for dysfunction manifest during **reperfusion**. These studies define a central and unifying role for **Egr-1** activation in the pathogenesis of **ischemic tissue** damage.

L14 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:759775 CAPLUS
DOCUMENT NUMBER: 136:52126
TITLE: Catalytic oligodeoxynucleotides define a key regulatory role for **early growth response factor**-1 in the porcine model of coronary in-stent restenosis
AUTHOR(S): Lowe, Harry C.; Fahmy, Roger G.; Kavurma, Mary M.; Baker, Andrew; Chesterman, Colin N.; Khachigian, Levon M.
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, University of South Wales and Prince of Wales Hospital, Sydney, NSW 2052, Australia
SOURCE: Circulation Research (2001), 89(8), 670-677
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Early growth response factor**-1 (Egr-1) controls the expression of a growing no. of genes involved in the pathogenesis of atherosclerosis and postangioplasty restenosis. Egr-1 is activated by diverse proatherogenic stimuli. As such, this transcription factor represents a key mol. target in efforts to control vascular lesion formation in humans. In this study, we have generated DNAzymes targeting specific sequences in human EGR-1 mRNA. These mols. cleave in vitro transcribed EGR-1 mRNA efficiently at preselected sites, inhibit EGR-1 protein expression in human aortic smooth muscle cells, block serum-inducible cell proliferation, and abrogate cellular regrowth after mech. injury in vitro. These DNAzymes also selectively inhibit EGR-1 expression and proliferation of porcine arterial smooth muscle cells and reduce intimal thickening after stenting pig coronary arteries in vivo. These findings demonstrate that endoluminally delivered DNAzymes targeting EGR-1 may serve as inhibitors of in-stent restenosis.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:728442 CAPLUS
DOCUMENT NUMBER: 132:48454
TITLE: New DNA enzyme targeting Egr-1 mRNA inhibits vascular smooth muscle proliferation and regrowth after injury
AUTHOR(S): Santiago, Fernando S.; Lowe, Harry C.; Kavurma, Mary M.; Chesterman, colin N.; Baker, Andrew; Atkins, David G.; Khachigian, Levon M.
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, The University of New South Wales and Prince of Wales Hospital, Sydney, Australia
SOURCE: Nature Medicine (New York) (1999), 5(11), 1264-1269
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Early growth response factor**-1 (Egr-1) binds to the promoters of many genes whose products influence cell movement and replication in the artery wall. Here the authors targeted Egr-1 using a new class of DNA-based enzyme that specifically cleaved Egr-1 mRNA, blocked induction of Egr-1 protein, and inhibited cell proliferation and wound repair in culture. The DNA enzyme also inhibited Egr-1 induction and neointima formation after balloon injury to the rat carotid artery wall. These findings demonstrate the utility of DNA enzymes as biol. tools to delineate the specific functions of a given gene, and implicate catalytic nucleic acid mols. composed entirely of DNA as potential therapeutic agents.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS

L8 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:58823 BIOSIS
DOCUMENT NUMBER: PREV200100058823
TITLE: **Egr-1**, a master switch coordinating upregulation of divergent gene families underlying ischemic stress.
AUTHOR(S): Yan, Shi-Fang (1); Fujita, Tomoyuki; Lu, Jiesheng; Okada, Kenji; Zou, Yu Shan; Mackman, Nigel; Pinsky, David J.; Stern, David M.
CORPORATE SOURCE: (1) Department of Surgery, Columbia University, 630 West 168th Street, New York, NY: sy18@columbia.edu USA
SOURCE: Nature Medicine, (December, 2000) Vol. 6, No. 12, pp. 1355-1361. print.
ISSN: 1078-8956.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Activation of the zinc-finger transcription factor early growth response (**Egr**)-**1**, initially linked to developmental processes, is shown here to function as a master switch activated by ischemia to trigger expression of pivotal regulators of inflammation, coagulation and vascular hyperpermeability. Chemokine, adhesion receptor, procoagulant and permeability-related genes are coordinately upregulated by rapid ischemia-mediated activation of **Egr-1**. Deletion of the gene encoding **Egr-1** strikingly diminished expression of these mediators of vascular injury in a murine model of lung ischemia/ **reperfusion**, and enhanced animal survival and organ function. Rapid activation of **Egr-1** in response to oxygen deprivation primes the vasculature for dysfunction manifest during **reperfusion**. These studies define a central and unifying role for **Egr-1** activation in the pathogenesis of **ischemic tissue** damage.

L8 ANSWER 2 OF 4 MEDLINE
ACCESSION NUMBER: 2001081642 MEDLINE
DOCUMENT NUMBER: 20553755 PubMed ID: 11100120
TITLE: **Egr-1**, a master switch coordinating upregulation of divergent gene families underlying ischemic stress.
COMMENT: Erratum in: Nat Med 2001 Apr;7(4):509
AUTHOR: Yan S F; Fujita T; Lu J; Okada K; Shan Zou Y; Mackman N; Pinsky D J; Stern D M
CORPORATE SOURCE: Department of Surgery, College of Physicians & Surgeons of Columbia University, 630 West 168th Street, New York, New York 10032, USA.
CONTRACT NUMBER: HL55397 (NHLBI)
HL59488 (NHLBI)
HL63967 (NHLBI)
SOURCE: NATURE MEDICINE, (2000 Dec) 6 (12) 1355-61.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010911
Entered Medline: 20010108
AB Activation of the zinc-finger transcription factor early growth response (**Egr**)-**1**, initially linked to developmental processes, is shown here to function as a master switch activated by ischemia to trigger expression of pivotal regulators of inflammation, coagulation and vascular hyperpermeability. Chemokine, adhesion receptor, procoagulant and permeability-related genes are coordinately upregulated by rapid

ischemia-mediated activation of **Egr-1**. Deletion of the gene encoding **Egr-1** strikingly diminished expression of these mediators of vascular injury in a murine model of lung ischemia/**reperfusion**, and enhanced animal survival and organ function. Rapid activation of **Egr-1** in response to oxygen deprivation primes the vasculature for dysfunction manifest during **reperfusion**. These studies define a central and unifying role for **Egr-1** activation in the pathogenesis of **ischemic tissue** damage.

L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:879210 CAPLUS
DOCUMENT NUMBER: 134:145578
TITLE: **Egr-1**, a master switch coordinating upregulation of divergent gene families underlying ischemic stress
AUTHOR(S): Yan, Shi-Fang; Fujita, Tomoyuki; Lu, Jiesheng; Okada, Kenji; Zou, Yu Shan; Mackman, Nigel; Pinsky, David J.; Stern, David M.
CORPORATE SOURCE: Departments of Surgery, Columbia University, New York, NY, 10032, USA
SOURCE: Nature Medicine (New York) (2000), 6(12), 1355-1361
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Activation of the zinc-finger transcription factor early growth response (**Egr**)**-1**, initially linked to developmental processes, is shown here to function as a master switch activated by ischemia to trigger expression of pivotal regulators of inflammation, coagulation and vascular hyperpermeability. Chemokine, adhesion receptor, procoagulant and permeability-related genes are coordinately upregulated by rapid ischemia-mediated activation of **Egr-1**. Deletion of the gene encoding **Egr-1** strikingly diminished expression of these mediators of vascular injury in a murine model of lung ischemia/**reperfusion**, and enhanced animal survival and organ function. Rapid activation of **Egr-1** in response to oxygen deprivation primes the vasculature for dysfunction manifest during **reperfusion**. These studies define a central and unifying role for **Egr-1** activation in the pathogenesis of **ischemic tissue** damage.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 4 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001000727 EMBASE
TITLE: **Egr-1**, a master switch coordinating upregulation of divergent gene families underlying ischemic stress.
AUTHOR: Yan S.-F.; Fujita T.; Lu J.; Okada K.; Yu Shan Zou; Mackman N.; Pinsky D.J.; Stern D.M.
CORPORATE SOURCE: S.-F. Yan, Departments of Surgery, 630 West 168th Street, New York, NY, United States. sy18@columbia.edu
SOURCE: Nature Medicine, (2000) 6/12 (1355-1361).
Refs: 50
ISSN: 1078-8956 CODEN: NAMEFI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Activation of the zinc-finger transcription factor early growth response (

Egr)-**1**, initially linked to developmental processes, is shown here to function as a master switch activated by ischemia to trigger expression of pivotal regulators of inflammation, coagulation and vascular hyperpermeability. Chemokine, adhesion receptor, procoagulant and permeability-related genes are coordinately upregulated by rapid ischemia-mediated activation of **Egr-1**. Deletion of the gene encoding **Egr-1** strikingly diminished expression of these mediators of vascular injury in a murine model of lung ischemia/ **reperfusion**, and enhanced animal survival and organ function. Rapid activation of **Egr-1** in response to oxygen deprivation primes the vasculature for dysfunction manifest during **reperfusion**. These studies define a central and unifying role for **Egr-1** activation in the pathogenesis of **ischemic tissue** damage.

L27 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:50857 CAPLUS
DOCUMENT NUMBER: 134:114297
TITLE: Heart disease diagnosis using methods for monitoring of Egr-1 and Egr-2 gene expression
INVENTOR(S): Einstein, Richard
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001004356	A1	20010118	WO 2000-US18923	20000712

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-142973P P 19990712
AB The invention relates to the changes in gene expression in ischemic heart **tissue** compared to normal heart **tissue**. Methods are described for diagnosing coronary artery disease (CAD) assocd. with **ischemia** by measuring the induction of **early growth response factor**-1 (Egr-1) and **early growth response factor**-2 (Egr-2) genes in nucleic acid samples from patients. Such measuring can serve as a predictor of the effects of post ischemic events, such as heart attack and myocardic infraction. Also described are methods of screening modulators of Egr-1 and/or Egr-2 induction. Further, forensic methods are described for detg. ischemic related pathol.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 2 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002395541 EMBASE
TITLE: Changes in differential gene expression because of warm **ischemia** time of radical prostatectomy specimens.
AUTHOR: Dash A.; Maine I.P.; Varambally S.; Shen R.; Chinnaiyan A.M.; Rubin M.A.
CORPORATE SOURCE: Dr. M.A. Rubin, Brigham/Women's Hospital, Pathology, 75 Francis Street, Boston, MA 02115, United States. marubin@partners.org
SOURCE: American Journal of Pathology, (1 Nov 2002) 161/5 (1743-1748).
Refs: 23
ISSN: 0002-9440 CODEN: AJPAA4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The expression of thousands of genes can be monitored simultaneously using cDNA microarray technology. This technology is being used to understand the complexity of human disease. One significant technical concern regards

potential alterations in gene expression because of the effect of **tissue ischemia**. This study evaluates the increase in the differential gene expression because of **tissue** processing time. To evaluate differential gene expression because of **ischemia** time, prostate samples were divided into five time points (0, 0.5, 1, 3, and 5 hours). Each time point consisted of a homogeneous mixture of 12 to 15 prostate **tissue** cubes (5 mm(3)). These **tissues** were maintained at room temperature until at the assigned time point the **tissue** was placed in OCT, flash frozen in liquid nitrogen, and stored at -80.degree.C until RNA extraction. RNA from each time point was hybridized against an aliquot of 0 time point RNA from the same prostate. Four prostate glands were used in parallel studies. M-A plots were graphed to compare variability between time point sample hybridizations. Statistical Analysis of Microarray software was used to identify genes overexpressed at the 1-hour time point versus the 0-hour time with statistically significance. Microarray analysis revealed only a small percentage of genes (<0.6%) from more than 9000 to demonstrate overexpression at the 1-hour time point. Among the 41 statistically significant named overexpressed genes at the 1-hour time point were early growth response 1 (EGR1), jun B proto-oncogene (jun B), jun D proto-oncogene (jun D), and activating transcription factor 3 (ATF3). Genes previously associated with prostate cancer did not have significantly altered expression with **ischemia** time. Increased EGR1 protein expression was confirmed by Western blot analysis. Microarray technology has opened the possibility of evaluating the expression of a multitude of genes simultaneously, however, the interpretation of this complex data needs to be assessed circumspectly using refined statistical methods. Because RNA expression represents the **tissue** response to insults such as **ischemia**, and is also sensitive to degradation, investigators need be mindful of confounding artifacts secondary to **tissue** processing. All attempts should be made to process **tissue** rapidly to ensure that the microarray gene profile accurately represents the state of the cells and confirmatory studies should be performed using alternative methods (eg, Northern blot analysis, Western blot, immunohistochemistry).

L27 ANSWER 3 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002194211 EMBASE
TITLE: Endothelial response to hypoxia: Physiologic adaptation and pathologic dysfunction.
AUTHOR: Ten V.S.; Pinsky D.J.
CORPORATE SOURCE: Dr. D.J. Pinsky, Columbia Univ.Coll. Physicians/Surg., Division of Cardiology, 630 W. 168th St., New York, NY 10032, United States. djp5@columbia.edu
SOURCE: Current Opinion in Critical Care, (2002) 8/3 (242-250). Refs: 64
ISSN: 1070-5295 CODEN: COCCF7
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB When subjected to a period of oxygen deprivation, endothelial cells exhibit a characteristic pattern of responses that can be considered either adaptive or pathologic, depending on the circumstances. In this review, the molecular basis for these responses is detailed. Hypoxia shifts the endothelial phenotype towards one in which anticoagulant properties are diminished, permeability and leukoadhesivity are increased, and proinflammatory features dominate the endovascular milieu. Of all the different points of intersection between the coagulation and inflammatory axes in the vasculature, perhaps most fundamentally, hypoxia alters several key transcriptional factors, including early growth response gene 1 (Egr1) and hypoxia-inducible factor (HIF) 1, which coordinate separate

programs of gene activation. The preponderance of forces in the hypoxic endovascular environment, perhaps designed as an evolutionary adaptation to oxygen deprivation, can trigger severe, pathologic, clinical consequences in the setting of **tissue ischemia**.

L29 ANSWER 1 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2001:58823 BIOSIS
DOCUMENT NUMBER: PREV200100058823
TITLE: **Egr-1**, a master switch coordinating upregulation of divergent gene families underlying ischemic stress.
AUTHOR(S): Yan, Shi-Fang (1); Fujita, Tomoyuki; Lu, Jiesheng; Okada, Kenji; Zou, Yu Shan; Mackman, Nigel; Pinsky, David J.; Stern, David M.
CORPORATE SOURCE: (1) Department of Surgery, Columbia University, 630 West 168th Street, New York, NY: syl8@columbia.edu USA
SOURCE: Nature Medicine, (December, 2000) Vol. 6, No. 12, pp. 1355-1361. print.
ISSN: 1078-8956.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Activation of the zinc-finger transcription factor early growth response (**Egr**)-**1**, initially linked to developmental processes, is shown here to function as a master switch activated by **ischemia** to trigger expression of pivotal regulators of inflammation, coagulation and vascular hyperpermeability. Chemokine, adhesion receptor, procoagulant and permeability-related genes are coordinately upregulated by rapid **ischemia**-mediated activation of **Egr-1**. Deletion of the gene encoding **Egr-1** strikingly diminished expression of these mediators of vascular injury in a murine model of lung **ischemia**/reperfusion, and enhanced animal survival and organ function. Rapid activation of **Egr-1** in response to oxygen deprivation primes the vasculature for dysfunction manifest during reperfusion. These studies define a central and unifying role for **Egr-1** activation in the pathogenesis of ischemic **tissue** damage.

L29 ANSWER 2 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2002:173896 BIOSIS
DOCUMENT NUMBER: PREV200200173896
TITLE: Gene expression profile in mouse myocardium after **ischemia**.
AUTHOR(S): Lyn, Deborah (1); Liu, Xiaowei; Bennett, Nicole A.; Emmett, Nerimiah L.
CORPORATE SOURCE: (1) Dept. of Biochemistry, Morehouse School of Medicine, 720 Westview Drive, Atlanta, GA, 30310: lyn@msm.edu USA
SOURCE: Physiological Genomics, (May, 2000) Vol. 2, pp. 93-100. http://www.physiolgenomics.org. print.
ISSN: 1094-8341.
DOCUMENT TYPE: Article
LANGUAGE: English
AB This study was designed to elaborate a molecular profile of expressed genes during ischemic injury to the mouse heart after surgical constriction of the left coronary artery without reperfusion. A mouse cDNA array containing 588 known genes was used to compare gene expression in heart RNA after 24-h **ischemia** with control **tissue**. Alterations in gene expression on the array were supported by relative reverse transcription-polymerase chain reaction analysis after timed periods of **ischemia**. Decreased levels of the cell cycle regulator p18ink4 and the oxidative responsive gene glutathione S-transferase were accompanied by an upregulation of the genes associated with cardiac muscle development, alpha-myosin heavy chain and fetal myosin alkali light chain. Other stress responses elicited by cardiac injury included an induction of **Egr-1** and Egr-3 transcription factors, as well as the apoptotic regulator Bax. Altogether, these findings indicate that expression of genes associated with a fetal

transcription program may be involved with the post ischemic remodeling process in heart ventricles.

L29 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
ACCESSION NUMBER: 1999:494774 BIOSIS
DOCUMENT NUMBER: PREV199900494774
TITLE: Hypoxia/hypoxemia-induced activation of the procoagulant pathways and the pathogenesis of **ischemia** -associated thrombosis.
AUTHOR(S): Yan, Shi-Fang (1); Mackman, Nigel; Kisiel, Walter; Stern, David M.; Pinsky, David J. (1)
CORPORATE SOURCE: (1) Departments of Physiology and Cellular Biophysics, P and S 17-401, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, NY USA
SOURCE: Arteriosclerosis Thrombosis and Vascular Biology, (Sept., 1999) Vol. 19, No. 9, pp. 2029-2035.
ISSN: 1079-5642.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although oxygen deprivation has long been associated with triggering of the procoagulant pathway and venous thrombosis, blood hypoxemia and stasis by themselves do not lead to fibrin formation. A pathway is outlined through which diminished levels of oxygen activate the transcription factor early growth response-1 (**Egr-1**) leading to de novo transcription/translation of **tissue** factor in mononuclear phagocytes and smooth muscle cells, which eventuates in vascular fibrin deposition. The procoagulant response is magnified by concomitant suppression of fibrinolysis by hypoxia-mediated upregulation of plasminogen activator inhibitor-1. These data add a new facet to the biology of thrombosis associated with hypoxemia/stasis and imply that interference with mechanisms causing **Egr-1** activation in response to oxygen deprivation might prevent vascular fibrin deposition occurring in **ischemia** without directly interfering with other pro/anticoagulant pathways.

L29 ANSWER 4 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
ACCESSION NUMBER: 1997:362862 BIOSIS
DOCUMENT NUMBER: PREV199799654795
TITLE: Expression of immediate early genes after cardioplegic arrest and reperfusion.
AUTHOR(S): Aebert, Hermann; Cornelius, Torsten; Ehr, Tobias; Holmer, Stephan R.; Birnbaum, Dietrich E.; Riegger, Guenter A. J.; Schunkert, Heribert
CORPORATE SOURCE: Dep. Thoracic and Cardiovascular Surgery, Regensburg Univ. Hosp., Franz-Josef-Strauss-Allee, D-93042 Regensburg Germany
SOURCE: Annals of Thoracic Surgery, (1997) Vol. 63, No. 6, pp. 1669-1675.
ISSN: 0003-4975.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Background. Induction of protooncogenes such as c-fos, c-jun, and **EGR-1** has been implicated in cellular growth and differentiation. Heat-shock proteins (HSPs) such as hsp 70 may mediate resistance to **ischemia** after heat shock and ischemic preconditioning. The effects of cardioplegia on the regulation of these immediate early genes are unclear. Methods. Isolated rat hearts were subjected to different cold (5 degree C) or normothermic (35 degree C) cardioplegic solutions and reperfused with normothermic Krebs-Henseleit buffer. Right atrial biopsy specimens from patients undergoing coronary

artery bypass grafting with cold cardioplegic arrest were taken before and after cardiopulmonary bypass. Analysis of immediate early gene messenger RNAs was performed using Northern blots. Related proteins were localized by immunohistochemistry. Results. In rat hearts, cold cardioplegia for 40 minutes with Bretschneider or St. Thomas' 11 solution followed by 40 minutes' reperfusion resulted in a significant increase in left ventricular c-fos, **EGR-1**, and c-jun messenger RNA levels (4.0-, 3.1-, and 3.0-fold, respectively, with Bretschneider solution and 3.7-, 2.8-, and 2.1-fold, respectively, with St. Thomas' II solution) compared with control hearts perfused at 35 degree C with Krebs-Henseleit buffer. Normothermic cardioplegia with St. Thomas' II solution was without effect, whereas sequential perfusion with Krebs-Henseleit buffer at 5 degree C and 35 degree C resulted in a similar increase in protooncogene messenger RNA levels. Only cold Bretschneider solution was related to a 5.2-fold induction of hsp 70 messenger RNA levels. Likewise, rat atrial **tissues** and samples from patients after cardiopulmonary bypass displayed a significant induction of these immediate early genes. Monoclonal antibodies against c-FOS and HSP 70 proteins stained nuclei and perinuclear spaces of endothelial cells and cardiac myocytes. Conclusions. Cold cardioplegic arrest and normothermic reperfusion are potent triggers for immediate early gene induction. Hypothermia emerged as the prime stimulus for the examined protooncogenes. In contrast, hsp 70 induction was dependent on the cardioplegic solution.

L29 ANSWER 5 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7

ACCESSION NUMBER: 1993:91805 BIOSIS
DOCUMENT NUMBER: PREV199395047001
TITLE: Proto-oncogene expression in porcine myocardium subjected to **ischemia** and reperfusion.
AUTHOR(S): Brand, Thomas (1); Sharma, Hari S.; Fleischmann, Kirsten E.; Duncker, Dirk J.; McFalls, Edward O.; Verdouw, Pieter D.; Schaper, Wolfgang
CORPORATE SOURCE: (1) Molecular Cardiology Unit, Baylor Coll. Med., One Baylor Plaza, Room 506 C, Houston, Tex. 77030
SOURCE: Circulation Research, (1992) Vol. 71, No. 6, pp. 1351-1360. ISSN: 0009-7330.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The molecular basis of myocardial adaptation to **ischemia** and reperfusion is poorly understood. It is thought that nuclear proto-oncogenes act as third messengers, converting cytoplasmic signal transduction into long-term changes of gene expression. We studied the expression of six nuclear proto-oncogenes (**Egr-1**, c-fos, fosB, c-jun, junB, and c-myc) in myocardium subjected to **ischemia** and reperfusion in anesthetized pigs. Stunning was achieved by two 10-minute left anterior descending coronary artery occlusions separated by 30 minutes of reperfusion. Hearts were excised after the first occlusion, after the first reperfusion, and at 30, 120, 150, and 210 minutes of reperfusion after the second occlusion. Total RNA was prepared from stunned as well as normally perfused myocardial **tissue** and subjected to Northern blotting. The response of the six nuclear proto-oncogenes varied. fosB gene expression was never detected. The c-myc gene was expressed, but its level was unchanged by **ischemia**. c-jun expression was slightly increased by **ischemia** (3.1+-0.6-fold). The c-fos, **Egr-1**, and junB genes were highly induced, being fivefold to sevenfold higher in experimental than in control **tissue**. In three animals pretreated with the beta-1-antagonist metoprolol and then subjected to the above experimental protocol, the induction of proto-oncogenes was similar to that in nonblocked controls. Our results show that the myocardial adaptive response to ischemic stress includes the induction of at least four transcription factors that may be further operative in repair processes and angiogenesis.

L29 ANSWER 6 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8
ACCESSION NUMBER: 1990:338643 BIOSIS
DOCUMENT NUMBER: BA90:46662
TITLE: CHANGES IN GENE EXPRESSION AFTER TEMPORARY RENAL **ISCHEMIA**.
AUTHOR(S): SAFIRSTEIN R; PRICE P M; SAGGI S J; HARRIS R C
CORPORATE SOURCE: MOUNT SINAI SCH. MED., 1 GUSTAVE L. LEVY PLACE, NEW YORK, N.Y. 10029, USA.
SOURCE: KIDNEY INT, (1990) 37 (6), 1515-1521.
CODEN: KDYIA5. ISSN: 0085-2538.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Temporary renal **ischemia** is followed by increased DNA synthesis and cell division as the kidney restores the continuity of the renal epithelium. We sought to characterize some of the changes in proto-oncogene and growth factor expression during this proliferative response. Northern analysis of polyadenylated RNAs of kidney cortical and outer stripe of outer medullary **tissue** from male Sprague-Dawley rats was performed following release of renal hilar clamping of 50 minutes duration. **Ischemia** produced an increase in c-fos mRNA that reached a peak at one hour and declined rapidly to control levels by four hours after release of the clamp. A similar rapid increase and decrease in early growth response 1 (**Egr 1**) mRNA was noted. The response of these immediate early genes was typical of their response to mitogens, suggesting that they served a similar role in renal cell regeneration. Levels of c-Ki-ras and glyceraldehyde phosphate dehydrogenase mRNA were unchanged. Renal preproEGF mRNA decreased at two hours, was virtually absent by 24 hours and remained low for at least four days after **ischemia**. Urinary excretion of EGF fell immediately after release of **ischemia** and before the decline in preproEGF mRNA or SNGFR, suggesting post-transcriptional affects of **ischemia** on renal EGF production. EGF excretion returned to only 50% of control by day 21. Specific 125I-EGF binding increased in membrane fractions of cortex, outer medulla and inner medulla as early as 24 hours after release of the clamp. Cortical 125I-EGF binding increased in the proximal tubule but not in the glomerulus. The later and more prolonged responses of the renal EGF system to **ischemia** may also be involved in the renal regenerative response. These observations help to identify several molecular events that accompany renal regeneration after ischemic injury.

L29 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9
ACCESSION NUMBER: 1990:197507 BIOSIS
DOCUMENT NUMBER: BA89:104178
TITLE: EXPRESSION OF TWO IMMEDIATE EARLY GENES **EGR-1** AND C-FOS IN RESPONSE TO RENAL **ISCHEMIA** AND DURING COMPENSATORY RENAL HYPERTROPHY IN MICE.
AUTHOR(S): OUELLETTE A J; MALT R A; SUKHATME V P; BONVENTRE J V
CORPORATE SOURCE: CELL BIOL. UNIT, SHRINERS BURNS INST., 51 BLOSSOM ST., BOSTON, MA 02114.
SOURCE: J CLIN INVEST, (1990) 85 (3), 766-771.
CODEN: JCINAO. ISSN: 0021-9738.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB To identify specific genetic regulatory mechanisms associated with renal **ischemia**, we measured the accumulation of **Egr-1** and c-fos mRNAs in the mouse kidney after occlusion of the renal artery and reperfusion. At 1 h after right nephrectomy and arterial occlusion of the contralateral kidney for 10 or 30 min, **Egr-1** mRNA levels were three to five times greater in these kidneys as compared with those in control animals that had sustained unilateral nephrectomy alone and were much greater than levels in the normal organ. Whether

ischemia was imposed for 10 or for 30 min, renal **Egr-1** mRNA contents were equivalent and remained elevated after 24 h of reperfusion subsequent to 30 min of **ischemia**. Although c-fos mRNA also accumulated in response to **ischemia** and reperfusion, the pattern differed from that of **Egr-1** in that c-fos mRNA content varied with the duration of **ischemia** and was undetectable 24 h after injury. Contralateral nephrectomy was not necessary to see the marked accumulation of **Egr-1** and c-fos mRNAs with unilateral **ischemia**. Reflow was necessary, however, since only minimal sequence accumulation occurred by the end of the ischemic period. After left uninephrectomy alone, Egr-I mRNA levels in the remaining kidney were maximal 30 min after surgery, but were not detectable thereafter; c-fos mRNA levels did not change after unilateral nephrectomy. Differential expression of early growth-related genes implicated in transcriptional activation may influence **tissue** recovery renal **ischemia**.

L29 ANSWER 8 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:264341 BIOSIS
DOCUMENT NUMBER: PREV200200264341
TITLE: Protein kinase C-beta deficiency attenuates lung **ischemia**/reperfusion injury.
AUTHOR(S): Yan, Shi-Fang (1); Fujita, Tomoyuki (1); Zou, Yu-shan; Pinsky, David J. (1); Stern, David M.
CORPORATE SOURCE: (1) Columbia Univ, New York, NY USA
SOURCE: Circulation, (October 23, 2001) Vol. 104, No. 17 Supplement, pp. II.529. http://circ.ahajournals.org/. print.
Meeting Info.: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L29 ANSWER 9 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:101572 BIOSIS
DOCUMENT NUMBER: PREV200100101572
TITLE: Early growth response-1 is a master switch in the pathogenesis of ischemic stress.
AUTHOR(S): Yan, Shi-Fang (1); Fujita, Tomoyuki (1); Okada, Kenji (1); Lu, Jiesheng (1); Zou, Yu Shan (1); Pinsky, David J. (1); Stern, David M. (1)
CORPORATE SOURCE: (1) Columbia Univ, New York, NY USA
SOURCE: Circulation, (October 31, 2000) Vol. 102, No. 18 Supplement, pp. II.371. print.
Meeting Info.: Abstracts from Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L29 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:25278 BIOSIS
DOCUMENT NUMBER: PREV200000025278
TITLE: Suppression of hypoxia-induced **tissue** factor expression in protein kinase C-betanull mice.
AUTHOR(S): Yan, Shi-Fang (1); Lu, Jiesheng (1); Zou, Yu Shan (1); Leitges, Michael; Kisiel, Walter; Stern, David M.
CORPORATE SOURCE: (1) Columbia Univ, New York, NY USA
SOURCE: Circulation, (Nov. 2, 1999) Vol. 110, No. 18 SUPPL., pp. I.746.
Meeting Info.: 72nd Scientific Sessions of the American

Heart Association Atlanta, Georgia, USA November 7-10, 1999
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L29 ANSWER 11 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:322461 BIOSIS
DOCUMENT NUMBER: BR39:29797
TITLE: LOCALIZATION OF THE **EGR-1** PROTEIN PRODUCT TO THE DISTAL NEPHRON AFTER RENAL **ISCHEMIA** AND REPERFUSION.
AUTHOR(S): BONVENTRE J V; OUELLETTE A J; SUKHATME V P; BROWN D
CORPORATE SOURCE: DEP. MED., MASS. GEN. HOSP., BOSTON, MASS.
SOURCE: MEETING OF THE ASSOCIATION OF AMERICAN PHYSICIANS, THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, AND THE AMERICAN FEDERATION FOR CLINICAL RESEARCH, WASHINGTON, D.C., USA, MAY 4-7, 1990. CLIN RES, (1990) 38 (2), 442A.
CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L29 ANSWER 12 OF 19 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999077713 MEDLINE
DOCUMENT NUMBER: 99077713 PubMed ID: 9858769
TITLE: Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins.
AUTHOR: Herdegen T; Leah J D
CORPORATE SOURCE: Institute of Pharmacology, University of Kiel, Hospitalstrasse 4, 24105, Kiel,. Germany.t.herdegen@pharmakologie.uni-kiel.de
SOURCE: BRAIN RESEARCH. BRAIN RESEARCH REVIEWS, (1998 Dec) 28 (3) 370-490. Ref: 1440
Journal code: 8908638. ISSN: 0165-0173.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990303

AB This article reviews findings up to the end of 1997 about the inducible transcription factors (ITFs) c-Jun, JunB, JunD, c-Fos, FosB, Fra-1, Fra-2, Krox-20 (Egr-2) and Krox-24 (NGFI-A, **Egr-1**, Zif268); and the constitutive transcription factors (CTFs) CREB, CREM, ATF-2 and SRF as they pertain to gene expression in the mammalian nervous system. In the first part we consider basic facts about the expression and activity of these transcription factors: the organization of the encoding genes and their promoters, the second messenger cascades converging on their regulatory promoter sites, the control of their transcription, the binding to dimeric partners and to specific DNA sequences, their trans-activation potential, and their posttranslational modifications. In the second part we describe the expression and possible roles of these transcription factors in neural **tissue**: in the quiescent brain, during pre- and postnatal development, following sensory stimulation, nerve transection (axotomy), neurodegeneration and apoptosis, hypoxia-**ischemia**, generalized and limbic seizures, long-term potentiation and learning, drug dependence and withdrawal, and following stimulation by neurotransmitters, hormones and neurotrophins. We also describe their expression and possible roles in glial cells. Finally, we discuss the

relevance of their expression for nervous system functioning under normal and patho-physiological conditions.

L29 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2001:922825 CAPLUS
DOCUMENT NUMBER: 137:149969
TITLE: Influence of Ginkgo Biloba extract (EGB 761) on expression of **EGR-1** mRNA and HSP-70 mRNA after warm **ischemia** in the rat liver
AUTHOR(S): Schutte, A.; Topp, S. A.; Knoefel, W. T.; Brilloff, S.; Mueller, L.; Rogiers, X.; Gundlach, M.
CORPORATE SOURCE: Department of Hepatobiliary and Transplant Surgery, University Hospital Eppendorf, Hamburg, Germany
SOURCE: Transplantation Proceedings (2001), 33(7-8), 3724-3725
CODEN: TRPPA8; ISSN: 0041-1345
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of the Ginkgo Biloba ext., EGB 761, on the expression of early growth response-1 (**EGR-1**) and heat-shock protein (HSP)-70 mRNA was evaluated. Liver **tissues** from Lewis rats were immediately snap frozen in liq. nitrogen and stored at -80.degree.. The pretreatment with EGB 761 resulted in an increased expression of HSP-70 and **EGR-1** mRNA in the rat liver after warm **ischemia** on the left liver lobe. It was hypothesized that the enhancing effects of EGB 761 on hepatic reperfusion injuries are enhanced by an increased HSP-70 expression after EGB 761 administration. EGB 761 enhanced **EGR-1** activity as evidenced by the increased mRNA expression, which could improve liver-regeneration after ischemic organ damage. EGB 761 could be a useful agent to attenuate postischemic reperfusion injuries, providing a variety of beneficial effects on hepatic microcirculation and liver regeneration.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:332435 CAPLUS
DOCUMENT NUMBER: 136:336850
TITLE: Drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis
INVENTOR(S): Wasylyk, Bohdan; Multon, Marie-Christine; Ayadi, Abdelkader; Zheng, Hong
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.; Institut National de la Sante et de la Recherche Medicale (INSERM)
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002035235	A2	20020502	WO 2001-EP12987	20011023

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1202065 A1 20020502 EP 2000-402968 20001025
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
AU 2002019086 A5 20020506 AU 2002-19086 20011023
PRIORITY APPLN. INFO.: EP 2000-402968 A 20001025
WO 2001-EP12987 W 20011023

AB The present invention relates to the regulation of the activity of mouse and human NET (ERP/SAP-2) transcription factors and to compds. which modify or regulate NET protein activity. The invention further relates to methods of screening for agonists or antagonists of NET in order to identify new pro-angiogenic or anti-angiogenic compds. and to therapeutic uses of these compds. The invention also relates to transgenic animals bearing mutations in NET gene.

L29 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:50857 CAPLUS
DOCUMENT NUMBER: 134:114297
TITLE: Heart disease diagnosis using methods for monitoring of **Egr-1** and Egr-2 gene expression
INVENTOR(S): Einstein, Richard
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001004356	A1	20010118	WO 2000-US18923	20000712

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-142973P P 19990712

AB The invention relates to the changes in gene expression in ischemic heart **tissue** compared to normal heart **tissue**. Methods are described for diagnosing coronary artery disease (CAD) assocd. with **ischemia** by measuring the induction of early growth response factor-1 (**Egr-1**) and early growth response factor-2 (Egr-2) genes in nucleic acid samples from patients. Such measuring can serve as a predictor of the effects of post ischemic events, such as heart attack and myocardic infraction. Also described are methods of screening modulators of **Egr-1** and/or Egr-2 induction. Further, forensic methods are described for detg. ischemic related pathol.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:611676 CAPLUS
DOCUMENT NUMBER: 130:23674
TITLE: Ischemic preconditioning and brain tolerance temporal histological and functional outcomes, protein synthesis requirement, and interleukin-1 receptor antagonist and early gene expression
AUTHOR(S): Barone, Frank C.; White, Raymond F.; Spera, Patricia A.; Ellison, Julie; Currie, R. William; Wang, Xinkang;

Feuerstein, Giora Z.
CORPORATE SOURCE: Department of Cardiovascular Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Stroke (1998), 29(9), 1937-1951
CODEN: SJCCA7; ISSN: 0039-2499
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A short duration of **ischemia** (ie, ischemic preconditioning [PC]) can provide significant brain protection to subsequent ischemic events (ie, ischemic tolerance [IT]). The present series of studies was conducted to characterize the temporal pattern of a PC paradigm, to systematically evaluate the importance of protein synthesis in PC-induced IT, and to explore candidate gene expression changes assocd. with IT. Temporary middle cerebral artery occlusion (MCAO) (10 min) was used for PC. Various periods of reperfusion (ie, 2, 6, and 12 h and 1, 2, 7, 14, and 21 days) were allowed after PC and before permanent MCAO (PMCAO) (n=7 to 9 per group) to establish IT compared with non-PC (sham-operated) rats (n=22). Infarct size, forelimb and hindlimb motor function, and cortical perfusion (laser-Doppler flowmetry; n=9 per group) were measured after PMCAO. The effects of the protein synthesis inhibitor cycloheximide administered just before PC (n=13 to 17) or administered long after PC but just before PMCAO (n=7 to 8) on IT were also detd. Interleukin-1 receptor antagonist mRNA (reverse transcriptase and polymerase chain reactions [n=20] and Northern anal. [n=50]) and protein expression (immunohistochem. [n=16]) after PC and early response gene expression (Northern anal. [n=16]) after PMCAO in PC animals were detd. Hemispheric infarct was significantly (P<0.01) reduced only if PC was performed 1 day (decreased 58.4%), 2 days (decreased 58.1%), or 7 days (decreased 59.4%) before PMCAO. PC significantly (P<0.01) reduced neurol. deficits (similar to redns. in infarct size). Cycloheximide eliminated ischemic PC-induced IT effects on both brain injury and neurol. deficits if administered before PC (P<0.05) but not if administered long after PC but before PMCAO. PC did not produce any significant brain injury, alter cortical blood flow after PMCAO, or produce contralateral cortical neuroprotection. Interleukin-1 receptor antagonist mRNA and protein expression were increased significantly (P<0.01) only during the IT period. PC rats also exhibited a significant (P<0.01) redn. in c-fos and zif268 mRNA expression after PMCAO. PC is a powerful inducer of ischemic brain tolerance as reflected by preservation of brain **tissue** and motor function. PC induces IT that is dependent on de novo protein synthesis. New protein(s) that occurs at the PC brain site 1 to 7 days after PC contributes to the neuroprotection. Those proteins that are produced after the more severe PMCAO in PC animals apparently do not contribute to IT. The PC-induced IT is also assocd. with increased expression of the neuroprotective protein interleukin-1 receptor antagonist and a reduced postischemic expression of the early response genes c-fos and zif268.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:322601 CAPLUS
DOCUMENT NUMBER: 125:7272
TITLE: Induction of immediate-early, ornithine decarboxylase and antizyme gene expression in the rat small intestine after transient **ischemia**
AUTHOR(S): Pujic, Z.; Matsumoto, I.; Yamataka, A.; Miyano, T.; Wilce, P.
CORPORATE SOURCE: Dep. of Biochemistry, Univ. of Queensland, St Lucia, 4072, Australia
SOURCE: Life Sciences (1996), 58(25), 2289-2296
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The expression of the immediate early genes (IEG)s c-fos, c-jun and zif/268, and the genes coding for ornithine decarboxylase (ODC) and its regulatory protein antizyme (AZ), was studied in rat small intestine following transient **ischemia**. The ischemic stimulus for 10 min alone did not alter the expression of these genes. A rapid and transitory induction of all IEG mRNAs occurred in a coordinated manner peaking at 30 min following recirculation and returned to basal levels 3 h after recirculation. Protein products of the IEGs accumulated in the smooth muscle layer of the intestine by 2-3 h after recirculation. Expression of both ODC and AZ mRNAs initially decreased to 70% of control levels 1 h after recirculation but markedly increased at 2 to 4 h after recirculation. The functional significance of these changes in gene expression in relation to **tissue** integrity and function after the **ischemia**/reperfusion is discussed.

L29 ANSWER 18 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002155333 EMBASE
TITLE: Myeloid differentiation (MyD)/growth arrest DNA damage (GADD) genes in tumor suppression, immunity and inflammation.
AUTHOR: Liebermann D.A.; Hoffman B.
CORPORATE SOURCE: D.A. Liebermann, Fels Institute for Cancer Research, Molecular Biology/Dept. of Biochem., Temple University School of Medicine, 3307 N Broad Street, Philadelphia, PA 19140, United States
SOURCE: Leukemia, (2002) 16/4 (527-541).
Refs: 226
ISSN: 0887-6924 CODEN: LEUKED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Myeloid differentiation (MyD) primary response and growth arrest DNA damage (Gadd) genes comprise a set of overlapping genes, including known (IRF-1, **EGR-1**, Jun) and novel (MyD88, Gadd45.alpha., MyD118/Gadd45.beta., GADD45.gamma., MyD116/Gadd34) genes, that have been cloned by virtue of being coordinately induced upon the onset of terminal myeloid differentiation and following exposure of cells to stress stimuli. In recent years it has become evident that MyD/Gadd play a role in blood cell development, where they function as positive regulators of terminal differentiation, lineage-specific blood cell development and control of blood cell homeostasis, including growth inhibition and apoptosis. MyD/Gadd are also involved in inflammatory responses to invading micro-organisms, and response to environmental stress and physiological stress, such as hypoxia, which results in ischemic **tissue** damage. An intricate network of interactions among MyD/GADD genes and gene products appears to control their diverse functions. Deregulated growth, increased cell survival, compromised differentiation and deficiencies in DNA repair are hallmarks of malignancy and its progression. Thus, the role MyD/Gadd play in negative growth control, including cell cycle arrest and apoptosis, and in DNA repair, make them attractive molecular targets for tumor suppression. The role MyD/Gadd play in innate immunity and host response to hypoxia also make these genes and gene products attractive molecular targets to treat immunity and inflammation disorders, such as septic shock and ischemic **tissue** damage.

L29 ANSWER 19 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999254395 EMBASE

TITLE: Induction of an immediate early gene **egr-1** by zinc through extracellular signal-regulated kinase activation in cortical culture: Its role in zinc-induced neuronal death.

AUTHOR: Jeong Ae Park; Koh J.-Y.

CORPORATE SOURCE: Dr. J.-Y. Koh, Natl. Creative Res. Initiative Ctr., Department of Neurology, Univ. of Ulsan College of Medicine, 388-1 Poongnap-Dong Songpa-Gu, Seoul 137-040, Korea, Republic of

SOURCE: Journal of Neurochemistry, (1999) 73/2 (450-456).
Refs: 34
ISSN: 0022-3042 CODEN: JONRA

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery

LANGUAGE: English

SUMMARY LANGUAGE: English

AB **Egr-1** is one of the immediate early transcription factors that are induced after brain insults. However, the mechanism and the role of **Egr-1** induction are not yet determined. In the present study, using mouse cortical cultures, we examined the ionic mechanism of **Egr-1** induction and its role in neuronal death. Although zinc, NMDA, or ionomycin induced comparable neuronal death in cortical culture, only zinc increased **Egr-1** expression, which was attenuated by blocking zinc influx. It is intriguing that brief exposure to zinc induced sustained extracellular signal-regulated kinase (Erk) activation. PD098059, an inhibitor of the Erk 1/2 upstream kinase mitogen- activated protein kinase kinase 1 (MEK1), blocked Erk 1/2 activation, **Egr-1** induction, and neuronal death by zinc. The present study has demonstrated that zinc, rather than calcium, induces lasting **Egr-1** expression in cortical culture by activating Erk 1/2, which is part of a cascade that may play an active role in zinc neurotoxicity. We propose that translocation of endogenous zinc may be the key mechanism of **Egr-1** induction and neuronal death in brain **ischemia**.